

Author Response 1

Thank you for the time and effort spent by the reviewers and editor to evaluate and give suggestions for our manuscript and also for the opportunity to revise our paper in this prestigious journal.

Response to Reviewer

Reviewer(s)' Comments to Author:

Reviewer: 1

Comments to the Author

This analysis offers important current information about the clinical course and the prognosis of severe SARS-Cov-2 induced disease.

Response: Thank you very much for reviewing our paper, providing us with constructive comments, and giving us opportunity to revise this paper.

However, I have some minor concerns:

The paper should be corrected and revised by a native speaker.

The clinical message is important in my opinion. I additionally suggest to discuss the different meanings and values of the laboratory parameters described in this paper.

D-Dimers, ferritine and PCT are associated with mortality, whereas CRP is not. PCT may indicate an additional bacterial infection and might be not elevated by the virus itself.

Please speculate why CRP is of less value regarding mortality?

Can you give a weight to the impact of the described biomarkers?

Response: Thank you very much for the suggestion, we have corrected and revised the grammar. We also included the hypothesis why CRP of less value CRP in mortality. In the clinical implication section, we added the value of CRP and D-dimer. Based on our systematic review and meta-analysis, we suggest using serum CRP, procalcitonin, and D-Dimer to predict poor outcome in COVID-19. Serum CRP could also be used to monitor disease improvement, serum procalcitonin for bacterial superinfection, and serum D-dimer for implying thrombin production.

Reviewer: 2

Comments to the Author

I consider that the idea that the manuscript manages is good, but I found some drawbacks that I describe below.

Response: Thank you for your time in reviewing our paper. We will try to revise as you recommended.

- The grammar and punctuation of the manuscript should be reviewed since I found some errors such as in the conclusion where you write "This meta-analysis showed that elevated serum CRP, PCT, D-Dimer, and higher serum ferritin was associated with composite poor outcome in patients with COVID-19 "where you should use "were" because the subject is plural. On line 20 of page 9 appears "... 63%, p = 0.006), However,", placing a comma instead of a period.

Response: Thank you for your suggestion. We have revised the grammar and punctuation.

- As you mention within its limitations, the fact that there are already articles describing CRP, PCT, D-Dimer and Ferritin as prognostic markers in severe COVID-19 disease, makes that your publication lose novelty. Although I consider that your analysis is broader since there are more publications where these markers are analyzed.

Response: Thank you for your advice. Although many publications have showed the benefit of this biomarker, but the sample size were relatively small. In our meta-analysis, we showed significant association but with more power due to bigger sample size. We also added the SROC analysis for several cut off values for these biomarkers that may be used in clinical practice.

- I consider that forest plots should not be cut so that it can be seen how much dispersion exists in the data

Response: Thank you for your recommendation. We changed the mean difference of serum ferritin to standardized mean difference so that the forest plot can be seen as a whole picture.

- Your discussion of the clinical implications is very limited and should be expanded. How can the four markers be used together? Would it be applicable with the use of corticosteroids or anti-coagulants? Are they also markers that a patient is improving?

Response: Thank you for your advice. We added some clinical implications for CRP and D-dimer which may directly be used by the clinicians. Additionally, the use of corticosteroid and anticoagulants were added in the discussion. The clinical application of using CRP as one of the markers for disease improvement (other than IL-6, which is beyond our discussion) is added into the discussion.